UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/506,666	10/27/2004	Sonia Escaich	BJS-1721-81	4976

23117 7590 12/10/2008

NIXON & VANDERHYE, PC
901 NORTH GLEBE ROAD, 11TH FLOOR
ARLINGTON, VA 22203

EXAMINER	
GANGLE, BRIAN J	
ART UNIT	PAPER NUMBER
1645	

MAIL DATE	DELIVERY MODE
12/10/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/506,666	ESCAICH, SONIA	
	Examiner	Art Unit	
	Brian J. Gangle	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 September 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *2,9-12,15,16 and 18-29* is/are pending in the application.

4a) Of the above claim(s) *15,20 and 21* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *2, 9-12, 16, 18-19, and 22-29* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *9/15/2008*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicant's remarks and amendment filed on 9/15/2008 are acknowledged. Claims 2, 9-11, 15-16, and 18-21 are amended. Claims 1, 3-8, 13-14, and 17 are cancelled. New claims 22-29 are added. Claims 2, 9-12, 15-16, and 18-29 are pending. Claims 15 and 20-21 are withdrawn as being drawn to non-elected inventions. Claims 2, 9-12, 16, 18-19, and 22-29 are currently under examination with regard to SEQ ID NO:134.

Priority

Applicant has requested that the examiner acknowledge that a certified copy of the priority document has been received. As applicant states on page 9 of their remarks, the office action dated 4/14/2008 indicates that the examiner has considered the priority document. In addition, the office action dated 1/17/2007 indicates, both in the text of the action and on the Office Action Summary sheet, that a certified copy of the priority document has been received. For applicant's benefit, this is restated again below:

As stated previously, acknowledgment is made of applicant's claim for foreign priority under 35 U.S.C. 119(a)-(d). The certified copy has been filed in parent Application No. EPS 02290556.6, filed on 3/6/2002. However, the priority document contains no reference to the sequence set forth in SEQ ID NO:134 and therefore fails to provide adequate support under 35 USC 112 for claims 10-12 of the instant application. Consequently, the filing date of PCT/EP03/02925 (3/6/2003) will be used in the determination of the availability of art under 102(b).

Information Disclosure Statement

The information disclosure statement filed 9/15/2008 has been considered. An initialed copy is enclosed.

Objections Withdrawn

The objection to claim 2 because the claim refers to B2/D isolates rather than to B2/D *E. coli* isolates, is withdrawn in light of applicant's amendment thereto.

The objection to claim 2 because the claim contains the phrase "testing the polypeptides for immunogenicity using animals models," is withdrawn in light of applicant's amendment thereto.

The objection to claims 9, 10, and 18 because the claims contain Markush language that is not proper, is withdrawn in light of applicant's amendment thereto.

Objections Maintained

The objection to claim 11 because the claim contains the word "aministerable," is maintained for the reasons set forth in the previous office action.

Applicant argues: that there are US Patents that have issued with the word "aministerable" in the claims.

Applicant's arguments have been fully considered and deemed non-persuasive.

It is well settled that whether similar claims have been allowed to others is immaterial. See In re Giolito, 530 F.2d 397, 188 USPQ 645 (CCPA 1976) and Ex parte Balzarini 21 USPQ2d 1892, 1897 (BPAI 1991). The fact that others have used an incorrectly spelled word does not make the usage correct. There is no such word as "administerable" in any English language dictionary. Applicant should correct the spelling of the word so that it reads "administrable." Appropriate correction is required.

Claim Rejections Withdrawn

The rejection of claims 9 and 18-19 under 35 U.S.C. 101, because the claimed invention is directed to non-statutory subject matter, is withdrawn in light of applicant's amendment thereto.

The rejection of claim 1 under 35 U.S.C. 112, second paragraph, as being rendered vague and indefinite by the phrase "polypeptides having SEQ ID NOs," is withdrawn. The cancellation of the claim renders the rejection moot.

The rejection of claim 2 under 35 U.S.C. 112, second paragraph, because it recites the limitation "the bacteria" in line 4, is withdrawn in light of applicant's amendment thereto.

Claim Rejections Maintained

35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 10-12, 16, and newly submitted claims 22-29 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement for essentially the reasons set forth in the previous office action for the reasons set forth in the previous office action in the rejection of claims 10-12 and 16. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Applicant argues:

1. That Durant shows that MPV41 protects mice from lethal challenge with ExPEC strain S26 and demonstrates that this antigen can induce an antibody response in the host. Applicant states that MPV41 has the same sequence, except for the first amino acid, as the instantly claimed SEQ ID NO:134. Applicant asserts that this shows that "the polypeptide having a sequence set forth in SEQ ID NO:134 is capable of providing a protective immune response."

Applicant's arguments have been fully considered and deemed non-persuasive.

Applicant correctly states that Durant shows that MPV41 protects mice from lethal challenge with ExPEC strain S26. This does not, however, correlate to enablement of the instant invention for multiple reasons. First, MPV41 was only demonstrated to protect mice from lethal challenge with ExPEC strain S26. There is no indication that the mice were protected from disease or that mice that had established disease had any alleviation of said disease, only that 50% of the mice did not die. There is no indication that any strain other than ExPEC strain S26 is affected by MPV41. There is no indication that MPV41 is specific to *E. coli* extra-intestinal

infections as required by the claims. In addition, MPV41 does not have the same sequence as SEQ ID NO:134 and does not meet the limitations of the claims. While there is only one amino acid difference between MPV41 and SEQ ID NO:134, it is well established (as set forth in the previous office action and reiterated below) that a change of a single amino acid can significantly alter the immune response generate by a given antigen. Finally, there is no indication than any fragment of SEQ ID NO:134 or MPV41 would provide protection against any disease.

As outlined previously, claims 10-12 are drawn to vaccine compositions specific to *E. coli* extra-intestinal infections comprising an effective amount of a polypeptide having the sequence of SEQ ID NO:134. Claim 16 is drawn to a composition comprising SEQ ID NO:134 or an antigenic fragment thereof, which alleviates, treats, and/or prevents undesirable growth of *E. coli*. Newly submitted claims 22-29 are also drawn to vaccine or pharmaceutical compositions.

To be a vaccine, the composition must elicit protective immunity, demonstrable by pathogen challenge experiments in a reasonable model system. The skilled artisan would clearly realize the critical deficiency of this specification with respect to vaccines. There is absolutely no demonstration of protective immunity upon administration, in any animal model of disease, of a polypeptide having the sequence of SEQ ID NO:134, or any antigenic fragment thereof. Therefore it is not clear that the described protein is capable of generating an active immune response such as an antibody response that protects the animal against any type of disease. Applicant has failed to demonstrate that the claimed polypeptide is capable of eliciting the claimed immune response (i.e. a directed and protective immune response specific to extra-intestinal *E. coli* infections, for claims 10-12). In fact, the specification does not show any evidence that SEQ ID NO:134 elicits any immune response at all. There is no information regarding the function of the protein, its location in the cell, or its immunogenicity. Due to this lack of information, one would not necessarily expect administration of the protein to result in an immune response directed against the microorganism, or particular infections caused by the microorganism. While the skill in the art of immunology is high, to date, prediction of a specific immune response for any given composition in any given animal is quite unpredictable. Moreover, protein chemistry is probably one of the most unpredictable areas of biotechnology. Consequently, the effects of sequence dissimilarities upon protein structure and function cannot

be predicted. Bowie *et al.* (Science, 1990, 247:1306-1310) teach that an amino acid sequence encodes a message that determines the shape and function of a protein and that it is the ability of these proteins to fold into unique three-dimensional structures that allows them to function, carry out the instructions of the genome **and form immunoepitopes**. Bowie *et al.* further teach that the problem of predicting protein structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein is extremely complex (column 1, page 1306). Bowie *et al.* further teach that while it is known that many amino acid substitutions are possible in any given protein, the position within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of maintaining function are limited. Certain positions in the sequence are critical to the three dimensional structure/function relationship and these regions can tolerate only conservative substitutions or no substitutions (column 2, page 1306). Additionally, as evidenced by Greenspan *et al.* (*Nature Biotechnology* **7**: 936-937, 1999), defining epitopes is not as easy as it seems. Greenspan *et al.* recommends defining an epitope by the structural characterization of the molecular interface between the antigen and the antibody is necessary to define an "epitope" (page 937, column 2). According to Greenspan *et al.*, an epitope will include residues that make contacts with a ligand, here the antibody, but are energetically neutral, or even destabilizing to binding. Furthermore, an epitope will not include any residue not contacted by the antibody, even though substitution of such a residue might profoundly affect binding. Accordingly, it follows that the immunoepitopes that can elicit a protective immune response to a given pathogen can only be identified empirically. This constitutes undue experimentation. Further, applicant has claimed a vaccine that is specific to *E. coli* extraintestinal infections. *E. coli* strains can be generally classified into commensal, intestinal pathogenic, and extra-intestinal pathogenic strains. While commensal and intestinal strains do not generally cause extra-intestinal disease, these strains are capable of causing disease outside the intestinal tract, especially when there are precipitating factors present, such as an indwelling foreign body or impairment of host defenses (Russo *et al.*, J. Infect. Dis., 181:1753-1754). The specification shows that extra-intestinal strains are responsible for the majority of extra-intestinal infections, and suggests that there are immunogenic markers specific to these strains. However, applicant has provided no means of producing a vaccine which is specific to all extra-intestinal *E. coli* infections. Even if the claimed polypeptide (SEQ

ID NO:134) were shown to be specific and protective against extra-intestinal strains of *E. coli* (which is has not), this polypeptide would not provide specific protection from all extra-intestinal infections caused by *E. coli*. Such a vaccine would provide no protection from strains other than extra-intestinal *E. coli* strains, even though "commensal" and "intestinal" strains could cause extra-intestinal disease. Moreover, the claims are drawn to a vaccine against sepsis, which encompasses protection from toxins produced by bacteria. The specification does not disclose any polypeptides which have been shown to protect against intoxication by *E. coli*.

Furthermore, claims 16, 25, and 29 are not limited to treatments in humans or animals. The claim encompasses treating or preventing any undesirable growth of *E. coli*. Since applicant's claims are directed toward polypeptides (which might or might not induce an appropriate immune response), one of skill in the art would have no expectation that administering an antigenic polypeptide, or fragment thereof, would in any way alter growth of *E. coli* in food or on surfaces.

Therefore, given the lack of success in the art, the lack of working examples commensurate in scope to the claimed invention and the unpredictability of the generation of protective immunity, the specification, as filed, does not provide enablement for the claims as drawn. Hence, the specification is not enabling.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

The rejection of claim 11 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention, is maintained for the reasons set forth in the previous office action.

Applicant argues: that one of ordinary skill will appreciate that compositions may be formulated differently depending on the treatment indication. For example, formulations for neonates are different that those for adults or children.

Applicant's arguments have been fully considered and deemed non-persuasive.

Applicant's arguments do not address the issue raised by the rejection. It is understood that different formulations are used for different populations or for different treatments.

However, the issue raised in the rejection is that vaccines are used to prevent disease and are administered before the disease is present. Treatment of disease occurs after one has already contracted a disease. Therefore, it is not clear what form of a vaccine is "administerable" for treatment of a disase.

As outlined previously, claim 11 is rendered vague and indefinite by the phrase "vaccine composition of claim 10 for in a form administerable for treatment of." Vaccines are used in the prevention of disease, thus it is not clear what form of a vaccine would be administrable for treatment of a disease.

35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-2, 9-12, 16, 18-19, and newly submitted claims 22-29 are rejected under 35 U.S.C. 102(b) as being anticipated by Bingen *et al.* (WO 01/066572 A2, IDS filed 9/7/2004) for the reasons set forth in the rejection of claims 1-2, 9-12, 16, and 18-19 in the previous office action.

Applicant argues:

1. That the claimed compositions require a pharmaceutically acceptable carrier which applicant's believe is not described in conjunction with SEQ ID NO:784 and/or require antigenic fragments of the sequence set forth in SEQ ID NO:134 which are not believed to be described in the prior art.

2. That the art provides evidence that the polypeptide having a sequence set forth in SEQ ID NO:134 is capable of providing a protective immune response.

Applicant's arguments have been fully considered and deemed non-persuasive.

Regarding argument 1, Bingen states on page 129, lines 5-6 that the compositions comprise one or more physiologically inert vehicles and any excipient suitable for the

pharmaceutical formulation. Also, SEQ ID NO:784 comprises antigenic fragments of SEQ ID NO:134.

Regarding argument 2, the enablement rejection has been addressed above. It is noted that applicant is arguing that Bingen shows that the claimed invention is enabled. For this to be the case, Bingen must have disclosed the claimed invention. Therefore, applicant is arguing that the instant rejection is proper.

As outlined previously, the instant claims are drawn to polypeptides having the sequence of SEQ ID NO:134 or antigenic fragments thereof (claims 1 and 9), where said polypeptides are isolated by sequence analysis and purification of the protein (claim 2); vaccine compositions specific to *E. coli* extra-intestinal infections, comprising an effective amount of a polypeptide having the sequence of SEQ ID NO:134 with a carrier (claim 10); wherein the vaccine is for preventing urinary system infections, pyelonephritis, sepsis, bacteremia, and neonatal meningitidis (claim 11); and wherein said vaccine is adapted to specific indication in combination with components directed against other bacteria, such as *S. aureus* or group B *Streptococcus* or other bacteria implicated in systemic infections (claim 12); and to pharmaceutical compositions for alleviating and/or preventing and/or treating an undesirable growth of *E. coli* comprising said polypeptide and a carrier (claim 16); as well as compositions comprising said polypeptide and a carrier (claims 18-19).

Bingen *et al.* disclose vaccine compositions for preventing *E. coli* infections, in particular, extra-intestinal *E. coli* infections, such as pyelonephritis, septicemia, and meningitis (see page 3, lines 25-34 and page 13, line 24 – page 14, line 4). Said vaccine composition comprises polypeptides with the sequence of ORF550, pos. 4761-6410 (which corresponds to the instantly claimed SEQ ID NO:134)(see page 24 of the sequence listing). Bingen *et al.* also disclose that their vaccine composition can comprise, in addition to the polypeptide, other agents useful for preventing, alleviating, and/or treating other infections (page 130, lines 5-20). With regard to claim 2, the instant claim constitutes Product-by-Process type claims. In Product-by-Process type claims, the process of producing the product is given no patentable weight since it does not impart novelty to a product when the product is taught by the prior art. See *In re Thorpe*, 227 USPQ 964 (CAFC 1985); *In re Marosi*, 218 USPQ 289, 292-293 (CAFC 1983) and *In re Brown*, 173 USPQ 685 (CCPA 1972).

Conclusion

No claim is allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brian J. Gangle whose telephone number is (571)272-1181. The examiner can normally be reached on M-F 7-3:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Robert Mondesi can be reached on 571-272-0956. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Brian J Gangle/
Examiner, Art Unit 1645

/Robert B Mondesi/
Supervisory Patent Examiner,
Art Unit 1645